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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/291,925	04/14/99	ASHKENAZI A	P1055R1

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EXAMINER	
ZEMAN, R	
ART UNIT	**PAPER NUMBER**
1645	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
09/291,925	Ashkenazi et al.
Examiner	**Art Unit**
Robert A. Zeman	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Aug 22, 2001* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) ☐ they raise the issue of new matter. (See NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

4. ☒ Applicant's reply has overcome the following rejection(s):
   see attached

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☐ affidavit, b) ☒ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   see attached

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

   Claim(s) allowed: _____

   Claim(s) objected to: _____

   Claim(s) rejected: *1-5 and 7-46*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☒ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). *16*.

11. ☐ Other:

ADVISORY ACTION

The amendment filed on 8-22-01 is acknowledged. Claims 25-26, 28-29 and 33 have been amended. Claims 1-5 and 7-46 are pending. With regard to claim 15, it was inadvertently omitted from the art rejections of record.

Claim Rejections Withdrawn

The rejection of claims 29 under 35 U.S.C. 112, second paragraph, as being indefinite by the use of the phrase "N-linked site at 14" is withdrawn in light of the amendment thereto.

The rejection of claims 33 under 35 U.S.C. 112, second paragraph, as being indefinite by the inconsistent use of the terms "segment" and "sequence" is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23 and 38 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the previous Office action in rejecting claim 23. In short, the specification, while being enabling for DNA constructs comprising a first DNA sequence encoding a precursor peptide and

a second DNA sequence operably linked to the first DNA segment, wherein the second DNA sequence encodes a heterologous glycosylation site **deletion** variant, does not reasonably provide enablement for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence operably linked to the first DNA sequence, wherein the second DNA segment encodes a heterologous glycosylation site **addition** or any other type of glycosylation site variant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues:

1. The specification provides both general and detailed support for adding a glycosylation site to a protein (page 2, lines 16-18, page 3 lines 1-10, page 7 lines 3-10 and 14-19, and at page 13 lines 1-16).

2. Specification **lists** many techniques (page 13, lines 1-16 and 20-25) which can be used for glycosylation site addition. Applicant further argues said techniques were well known in the art at the time the application was filed and hence undue experimentation would not be necessary for creating a glycosylation site addition variant.

3. Applicant argues that the references cited on Paper No. 16, as well as the materials and methods section of the specification describe a process for adding glycosylation sites via site-directed mutagenesis.

4. Evidence provided by Applicant need not be conclusive but merely convincing to one of skill in the art the therefore the specification, as filed, fully supports the claims reciting glycosylation site addition variants.

Applicant's arguments have been fully considered and are deemed to be non-persuasive.

It should be noted that Applicant's citations of passages within the Specification do not correspond to the Specification of record (i.e. the substitute specification filed on 3-2-01) but to the Specification originally filed with the instant application.

As outlined in the previous Office action, the specification provides great detail on the construction and use of DNA comprising a first DNA sequence comprising a precursor peptide (the pro sequence of t-PA) which is operably linked to a second DNA sequence encoding a heterologous glycoprotein (TNFR1-IgG1). The specification further discloses the use of sequences for glycosylation site variants as the second DNA sequence and methods for the recombinant expression of said DNA constructs *in vitro*. The specification provides great detail in the methods required for the manufacture and use of DNA sequences encoding a heterologous glycosylation site **deletion** variant. The specification discloses that the chimeric proteins generated by the DNA constructs of the instant application contain 4 N-linked glycosylation sites (at amino acid positions 14, 105, 111 and 248) and that said glycosylation sites were "**deleted**" by replacing the codon specifying asparagine in the N-linked carbohydrate attachment sequence with codons specifying glutamine, aspartic acid, asparagine, lysine, serine or threonine thus inactivating the site (see pages 17 and 19). The specification discloses a myriad of different

glycosylation site mutants and their secretion efficiencies. However, all the disclosed variants are glycosylation site **deletion** variants. None of the disclosed variants contain more than the 4 N-linked glycosylation sites at amino acid positions 14, 105, 111 and 248. The specification is silent not only on where the additional sites would be located but also on the methods that would be used to achieve such a site addition. Consequently, it would require **undue** experimentation by one of skill in the art to make and use the claimed invention due to the total lack of guidance within the specification.

The portions of the specification cited by Applicant merely prophetically describe glycosylation site addition variants but fails to provide guidance on how to make said variants.

The references cited by Applicant describe methods of adding glycosylation sites to various proteins but not the proteins of the instant invention. Therefore the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make and use** the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 2-4 and 10-13 under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) is maintained for reasons of record.

Applicant argues:

1. There is no motivation to combine the cited references.

2. Foster et al. do not discuss the secretion of immunoadhesins or that a sequence including a pro-sequence of a mammalian t-PA could provide for secretion of an immunoadhesin or any other protein.

4. Foster et al. merely demonstrates that substituting the t-PA secretory peptide increased protein expression 5-10 fold.

5. Ashkenazi et al. do not discuss or suggest that TNFR-IgG is problematic or needs to be increased or that such an increase can be accomplished by including a t-PA pro-sequence.

6. Neither Foster et al. or Ashkenazi et al. do not discuss secretion of immunoadhesins or the need to change the level of secretion of said protein.

7. The instant invention provides unexpected results regarding the secretion of glycoproteins providing additional evidence that the claimed invention is not obvious of the combination of Foster et al. and Ashkenazi et al.

Applicant's arguments have been fully considered and are deemed to be non-persuasive.

As outlined in the previous Office Action, the instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). The disclosure by Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Ashkenazi et al., disclose the sequence for the TNFR-IgG1.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA chimeras disclosed by Foster et al. It is standard practice to maximize yields.

With regard to Applicant's assertion of **unexpected results**, it is noted that no factual evidence of such results has been presented. Arguments and assertions do not substitute for factual evidence.

Claims 2-5, 7-13, 15, 34-37 and 39-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) and Rickles et al. (Journal of Biological Chemistry Vol 263, No. 3 pages 1563-1569, 1988, IDS-5) for the reasons stated in the previous Office Action in rejecting claims 1-13.

Applicant argues:

1. The deficiencies of Foster et al. and Ashkenazi et al. are not remedied by Rickles et al.

2. Rickles et al. is directed to the isolation and purification of a cDNA encoding a murine tissue plasminogen activator. Said reference does not discuss or suggest that a sequence including a pro-sequence of a mammalian t-PA can or should be used to provide for secretion of any protein.

3. There is no discussion or suggestion that the pro-sequence of a mammalian t-PA sequence be operably linked to a non-mammalian t-PA pre-sequence.

4. There is no motivation to combine the aforementioned references.

Applicants arguments have been fully considered and are deemed to be non-persuasive.

Applicant is reminded that the aforementioned rejection is based on the **combination** of the cited references.

As outlined in the previous Office Action, the instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of non-mammalian t-PA. Ashkenazi et al. disclose the sequence for the TNFR-IgG1. Rickles et al. disclose the sequences for and the uses of murine t-PA in the molecular cloning of complementary DNA. Since Foster et al. disclose that **t-PAs from non-human sources** can be used in their method, and even listed an example (see column 9 lines 5-9) , it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment and the non-mammalian t-PA prosequence disclosed by Rickles et al in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since Foster et al. disclose that **t-PAs from non-human sources** can be used in their method, and even listed an example (see column 9 lines 5-9) it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment and the non-mammalian t-PA prosequence disclosed by Rickles et al in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al.

Claims 2-4, 10-14 and 16-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) and Berman and Lasky et al. (Trends in Biotechnology, Vol. 3, No. 2, pages 51-53, 1985, IDS-5) for the reasons stated in the previous Office Action in rejecting claims 1-4, 10-14, 16-22, and 23-33.

Applicant argues:

1. Berman and Lasky do not discuss the problems of secretion of glycoproteins or that a prosequence of a mammalian t-PA be operably linked to a DNA segment encoding an immunoadhesin or operably linked to a pre-sequence other than a mammalian t-PA pre-sequence.

2. Berman and Lasky do not teach or suggest the formation of glycosylation site variants.

3. One of skill in the art would not combine the teachings of the cited references.

Applicant's arguments have been fully considered and deemed to be non-persuasive. Applicant is reminded that the aforementioned rejection is based on the **combination** of the cited references. As outlined in the previous Office Action, Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). The disclosure by Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of glycosylation site variants as the products of the second DNA fragments. Ashkenazi et al. not only discloses the sequence for the TNFR-IgG1, but also potential asparagine-linked (N-linked) glycosylation sites (see Figure 1 on page 10536). Since, as disclosed by Berman and Lasky, N-linked glycosylation plays a role in the solubility half-life and antigenicity of the glycoprotein, it would have been obvious for one of skill in the art to alter the codons for the potential N-linked glycosylation sites in the sequence for TNFR-IgG1 (disclosed by Ashkenazi et al.) and use the resulting sequences as the second DNA segment in the constructs disclosed by Foster et al. The use of the aforementioned "TNFR-IgG1 glycosylation

variants" would not only take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al. but would allow for the rapid development of recombinant TNFR-IgG1 protein with tailored solubility, half-life and antigenicity properties.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032 or the examiner's supervisor, Lynette Smith, can be reached at (703)308-3909.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman

September 13, 2001